Summary

The subject of this thesis is introduced in *Chapter 1*. Parkinson's disease (PD) is a movement disorder which is characterized by motor symptoms, such as bradykinesia, tremor and rigidity. PD is caused by a progressive degeneration of dopamine producing neurons in the substantia nigra pars compacta (SNc). The SNc mainly projects to the striatum and interferes with the circuits between the striatum and the frontal cortex. Besides motor symptoms cognitive impairments and depression are often present. In the studies included in this thesis cognitive functioning and depression in PD are investigated using neuroimaging and clinical methods.

In PD cognitive impairments can be found in both automatic and controlled processing. Automatic processes take advantage of previously established and learned relationships between external or internal contexts and behavioral patterns. Controlled processing on the other hand, involves deliberate planning and regulation in new situations where current schemata are not sufficient. Concerning automatic processing, PD patients show difficulties with applying learned motor and cognitive skills and in learning new automaticities or skills. Feedback plays an important role in learning. However, in the context of feedback processing, and the influence of an altered feedback processing on the behavior of PD patients not many studies have been performed.

Besides impairments of automatic processing, PD patients also show impairments of controlled processing. Cognitive control or executive functions are assumed to have a number of constituent elementary functions, like monitoring, planning, inhibition, set-shifting and divided attention. Declarative memory, working memory and prospective memory also play an important role. In PD, impairments in cognitive flexibility, planning, working memory, inhibition and declarative memory have been reported.

Depression is another non-motor symptom that is common in PD. The diagnosis of depression in PD may however be difficult to establish. This is mainly caused by the fact that somatic symptoms also contribute to the diagnosis of depression in PD, which documents an overlap of symptoms of depression and PD. Consequently, depression can be overrated and underrated in PD. For clinical purposes it is therefore important to evaluate the depression rating scale scores on item level and considering which items are likely to be confounded by somatic symptoms or cognitive impairments.

Depression can also have a negative influence on cognitive functioning in PD. Studies focused on the relationship between depression and cognition in PD however show many discrepancies and often only cognitive screening scales are used. Attempts should therefore be taken to study the influence of depression on cognition in PD more extensively.

In the study described in *Chapter 2* it is investigated to what extent the overlapping symptoms of depression and PD are associated with the dopaminergic dysfunction of the striatum, which is typical for PD.

In our study it is shown that the dopaminergic dysfunction of the striatum, which is typical for PD, can cause symptoms that can also be categorized as symptoms of depression. Especially cognitive symptoms measured by a depression rating scale may be based on the dopaminergic dysfunction of the striatum in PD patients. Also, the motor and reward related aspects of depression might be based on the dopaminergic dysfunction in PD. Clinically these results imply that when assessing depression in PD one should be aware of a confounding influence of the symptoms of PD.

Depression rating scales used in PD, such as the Montgomery-Åsberg Depression Rating Scale (MADRS) measure affective, cognitive and somatic symptoms. An important clinical question, which is adressed in *Chapter 3*, is therefore which items of the MADRS are likely to be influenced by the motor symptoms of PD.

Our results indicate that the MADRS does measure more that just depression in PD. Especially, the items reflecting sleep problems and fatigue are likely to be influenced by motor symptoms of PD. This is consistent with previous studies reporting nocturnal difficulties in PD such as an inability to turn or getting out of bed. Also, fatigue is a common phenomenon in PD. Depression and PD thus cannot be considered as two separate syndromes due to the symptomatic overlap. It is however still important to recognize a depression in PD patients. In this matter it is important to qualitatively describe the answers of PD patients on the items of the depression rating scale. In addition, adjusted cut-off scores are required.

In *Chapter 4* evidence is reviewed with regard to impaired automatic and controlled information processing in cognitive functioning of PD patients, using a comprehensive mental schema framework, which comprises both motivational and cognitive elements.

It is concluded that the cognitive impairments observed in PD, both at the level of controlled and automatic processing, are the result of a complex interplay between the dopaminergic dysfunction of the fronto-striatal circuits, compensatory mechanisms and treatment strategies applied in PD.

In everyday life positive feedbacks in response to human action are an obvious phenomenon. In PD the striatal dysfunction impairs motor performance, but also may lead

to decreased positive feedback (reward) processing. In the study described in *Chapter 5* the consequences of dysfunctional fronto-striatal circuits in PD for the processing of positive feedback are investigated.

Our results reveal that the striatum is involved in positive feedback processing in healthy controls. In PD the striatum was not involved in positive feedback processing. Instead, PD patients showed increased prefrontal involvement during positive feedback processing. Positive feedback processing is thus altered in PD and is reflected by increased prefrontal involvement.

Positive feedback processing is thought to be associated with a behavioral trait called Novelty Seeking (NS). NS is 'a heritable tendency toward intense exhilaration or excitement in response to novel stimuli, cues for potential rewards or potential relief of punishment, which leads to frequent exploratory activity in pursuit of potential rewards as well as active avoidance of monotony and potential punishment'. In the study described in *Chapter 6* it was investigated whether PD patients show decreased levels of NS. In addition, it was investigated to what extent NS was associated with an altered positive feedback processing in PD.

Our findings show that in healthy controls NS is associated with positive feedback processing in the striatum. PD patients do not show decreased levels of NS. However, NS is not mediated by the striatum in PD. Instead, NS is (partly) mediated by the prefrontal cortex in PD, which provides a compensatory mechanism for positive feedback processing in PD. This suggests that the fronto-striatal dysfunction in PD does not necessarily changes behavioral traits. Instead behavioral traits appear to manifest themselves via other brain structures.

In the study described in *Chapter 7* controlled behavior in PD is investigated by focusing on the initiation of behavior, everyday planning and multi-task performance of PD patients and healthy controls, using the recently developed Cognitive Effort Test (CET). The CET is a relatively unstructured multiple component visual motor task from which three variables are derived, Initiative, Planning and Multi-task performance. It was also investigated to what extent the initiation of behavior, planning and multi-tasking of PD patients was influenced by more elementary executive functions (e.g. cognitive flexibility, inhibition and working memory).

PD patients did not show impairments in initiating behavior compared to healthy controls. They did however, tend to plan sequential, instead of simultaneous task performance. This

difference in planning does not indicate a specific impairment of planning but rather reflects a compensation for a decreased psychomotor speed. In addition, PD patients also actually performed tasks sequentially instead of simultaneously. This 'choice' appeared to be significantly influenced by a decreased attentional flexibility.

Two frequently observed non-motor symptoms in PD are depression and cognitive impairments, especially executive dysfunctions and memory impairments. Often these symptoms occur together in PD, but in patients with major depression without PD impairments in executive functions and memory have also been reported. Depression in PD might therefore exacerbate cognitive symptoms. The aim of the study described in *Chapter 8* was to investigate the influence of depression on cognition in PD specifically on the impairments in executive functions and memory.

Depressed PD patients did not show a significantly decreased performance on the executive functioning and memory tests, compared to non-depressed PD patients. However, depressed PD patients reported significantly more dysexecutive problems in daily life. Depression thus appears to influence cognition in PD negatively, mainly in the experience of depressed PD patients. In addition it is important to note that the tests used to assess cognitive control or executive functions are often structured and offer a standardized method, while cognitive control or executive functions are needed in situations which are unstructured and unstandardized. To gain more knowledge about the executive impairments that PD patients experience in daily life and the influence of depression on these impairments, unstructured tests are required.

In *Chapter 9* the results of the above described studies are discussed and conclusion are drawn. Our studies show that PD is a heterogeneous disease, many motor, cognitive and emotional symptoms are associated or overlap. These associations occur both within domains of impairment as well as between domains of impairments. It is therefore difficult to determine which impairments are primary and which are secondary in PD. Within the motor domain and the domain of cognition PD patients show deautomatisation and difficulties achieving automaticities. PD patients however, compensate by showing an increased involvement of the prefrontal cortex, which indicates that they show an increased reliance on cognitive control and a decreased reliance on automatic processing. The shift from automatic to controlled processing indicates however that if there is something wrong with automatic information processing this will also affect controlled processing. This suggests that impairments in the subprocesses of controlled processing are secondary to impairments in automatic processing.

Depression is another domain of impairment in PD. Depression may have a negative influence on cognition in PD. However, both cognitive impairments and motor symptoms can also influence the assessment of depression in PD, since these cognitive impairments and motor symptoms can be part of both PD and primary depression. The diagnosis of depression in PD thus needs to be carefully considered.